REMARKS

Applicant thanks the Examiner for entry of applicant's amendment filed on March 18, 2008. Claims 1, 2, 4-18, 21-33, 35, 36, 38-40, 43, 45, 48-61, 64-79, 82-85, 88, 91-96, 98, 100-109, and 112-121 are pending. Claims 2, 4-10, 12, 13, 33, 35, 36, 40, 48-50, 71-75, 78, 79, 91-94, 98, 100-102, 105 and 106 are withdrawn from consideration. Claims 1, 11, 14-18, 21-32, 38-39, 43, 45, 51-61, 64-70, 76-77, 82-85, 88, 95-96, 103-104, 107-109, and 112-121 are under consideration.

Applicant acknowledges that certain arguments presented in the amendment filed on March 18, 2008 have been found persuasive by the Examiner and that the rejections and/or objections not reiterated from the previous Office Actions are withdrawn, including specifically the rejection of claims 1, 11, 14, 16-18, 27, 29, 31, 43, 45, 51-55, 57-59, 82-85, 103, 104, 107, 108, 111 and 116 under 35 U.S.C. 102(a) over Levine, J.D., US 2004/0180916.

Rejections under 35 U.S.C. § 112

Claims 1, 11, 14-32, 38, 39, 42, 43, 51, 56-70, 76, 77, 113 and 115 are rejected under 35 USC section 112, first paragraph, as failing to comply with the written description requirement. Applicant disagrees with the Examiner's rejection and requests reconsideration.

The Examiner appears to agree that constipation-predominant IBS would correlate with an increase in gut transit time. In other words, constipation-predominant IBS would correlate with *slowing down* transit of material through the gut. The specification has a written description of treatment with methylnaltrexone to decrease gut transit time. In other words, the specification teaches that methylnaltrexone *speeds up* transit of material through the gut. According to the specification, constipation-predominant IBS (which is correlated with slowing down transit of material though the gut) is treated with methylnaltrexone (which speeds up transit of material through the gut).

One of ordinary skill in the art would understand from the relevant art that, as taught in the present specification, slower gut transit is an element of constipation-predominant IBS. As explained in Hutchinson et al., increased oral-cecal transit time is one of the symptoms of IBS[1]. Increased oral-cecal transit time, of course, means that material takes a longer time to move through

[1] Hutchinson R. et al, Gut, 1995; 35: 585-589

the gut. The specification contains data showing that methylnaltrexone can speed up transit of material through the gut in subjects not receiving exogenous opioids. Example 1 of the instant specification shows that the administration of methylnaltrexone in 12 normal subjects (8 male and 4 female) who were not receiving exogenous opioids significantly reduced oral-cecal transit time. In other words, methylnaltrexone caused material to move more quickly through the gut.

The Examiner stresses in the Office Action that the present rejection is a *written description* rejection. Notwithstanding, it would appear that the basis of the Examiner's rejection is that there is no experiment in the specification demonstrating success in a subject who actually has IBS. Respectfully, compliance with the written description requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an actual example of treatment of IBS is disclosed. As stated in the MPEP, possession of the invention may be shown in the absence of an actual working example by showing that the invention was "ready for patenting". As stated in the MPEP, an objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed."[2] To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed.

The present specification states unambiguously that constipation-predominant IBS can be treated with methylnaltrexone. (For example, see paragraph [0033] of the published specification). The present specification teaches that a symptom of IBS is slower transit of material through the gut. (For example, see paragraph [0019] of the published specification.) The present specification teaches that methylnaltrexone speeds up transit of material through the gut in subjects not receiving exogenous opioids. (For example, see Example 1 of the published specification.) The modes of administration, formulations including their manufacture, effective amounts and dosages of methylnaltrexone to be used in the treatment of IBS according to the methods of invention are described. (For example, see paragraphs [0025-0032, 0037-0039, 0091-0144] and Examples 2-5 of the published specification.) The specification provides sufficient description of the instant

[2] *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

invention to reasonably convey to the skilled artisan that the Applicant at the time of the filing of the present application had possession of the claimed invention.

The Examiner, respectfully, has not made a *prima facie* case for rejecting the claims on the basis of a lack of written description by simply pointing to the absence of an actual working example involving a diseased subject. The Examiner has not offered any reason why the experimental data presented, taken with the rest of the specification, would fail to convey to one of ordinary skill in the art that the applicant had possession of the invention at the time of filing the application. It is requested that the rejection on the basis of written description be withdrawn.

Double patenting

Claims 88, 93, 95, 96, 103, 104, 107-114 and 116-121 are provisionally rejected on the ground of non-statutory obviousness type double patenting as being unpatentable over claims 13-29, 32, 33 and 39-44 Co-Pending Application Number 11/441452. Applicant understands that in accordance with section 804 of the MPEP, a "provisional" double patenting rejection will continue to be made by the Examiner until the "provisional" double patenting rejection is the only rejection remaining in one of the applications. Accordingly, Applicant will address the appropriateness of these "provisional" double patenting rejections after the Examiner withdraws all other reasons for rejection.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 11, 14-27, 29-32, 38, 39. 42, 44-45, 51-68,70, 76, 77, 82-85, 88, 93, 95, 96, 103, 104, 107, 108, and 110-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levine, J.D. US 2004/0180916 (herein after Levine) in view of The Merck Manual, and De Schryver et al., *Scand. J. Gastroenterology.* Applicants respectfully request reconsideration of the rejection, because the cited Levine reference actually teaches away from the presently claimed invention. Applicant also requests withdrawal of the finality of the present office action because the new office action presents an entirely different rationale for rejecting the claims not necessitated by any amendment.

In the office action dated September 14, 2007, the present claims were rejected on the basis that "Levine teaches the administration of the specific [mu] opioid antagonist methylnaltrexone in combination with a [kappa]-opioid receptor antagonist to treat pain associated with IBS." (Office Action dated 9/14/2007, page 6, lines 7-9). The Examiner now agrees that the Levine priority document does not teach the administration of methylnaltrexone to treat pain associated with IBS. The Examiner, however, asserts in the present office action an entirely new argument in rejecting the claims. The Examiner states, "[b]ecause "methylnaltrexone does not cross the blood brain barrier, motivation is provided to select methylnaltrexone in place of naltrexone."

In connection with this new rejection, the Examiner, respectfully, has not presented a *prima facie* basis for rejecting the claims, because the cited reference itself unambiguously teaches away from the very substitution suggested by the Examiner. Quoting from the cited Levine provisional application:

> "The present invention provides methods...comprising administration of a centrally acting (i.e., crosses the blood brain barrier) agonist of a k opioid receptor and a **centrally acting opioid antagonist**...(page 2, lines 13-20)... The **opioid antagonist is also centrally acting** ...(page 3, line 6)....The **opioid antagonist preferably is a non-selective opioid antagonist,** i.e., a compound that antagonizes at least k, m, and d opioid receptors."(page 3, 7-8) [Emphasis added]

The Levine provisional teaches specifically that a centrally acting opioid antagonist is to be used. As acknowledged by the Examiner, Levine teaches that methylnatrexone does not pass the blood brain barrier and is therefore not a centrally acting opioid antagonist. Furthermore, the Levine provisional teaches that preferred antagonists are non-selective opioid antagonists. In contrast, it is well settled that methylnaltrexone is a selective mu-opioid receptor antagonist. The Levine provisional, therefore, unambiguously teaches away from the substitution suggested by the Examiner.

Respectfully, the Examiner has not made out a *prima facie* case for rejecting the claims on the basis of the Levine provisional. Contrary to the Examiner's assertion, there would have been no motivation to substitute methylnaltrexone, which is a peripherally restricted and selective mu

opioid receptor antagonist, for one of the centrally acting opioid antagonists taught by Levine. Indeed, the Levine provisional only teaches that the opioid antagonist should be both centrally acting and non-selective. The other cited references do not remedy these deficiencies in the Levine provisional. The Examiner appears to be relying on impermissible hindsight to make the rejection, and Applicant respectfully requests withdrawal of the rejection.

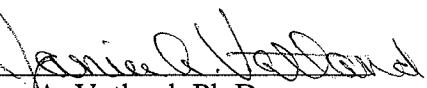
CONCLUSION

Claims 1, 11, 14-18, 21-32, 38-39, 43, 45, 51-61, 64-70, 76-77, 82-85, 88, 93, 95-96, 103-104, 107-109 and 112-121 are under examination. In view of the foregoing remarks, it is requested that the rejections under 35 U.S.C. sections 112 and 103 be withdrawn. If the Examiner believes, after this amendment, that a telephone call with the undersigned would advance prosecution of this application, the Examiner is requested to call the undersigned at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: December 12, 2008

Respectfully submitted,

By 

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